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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,502	10/09/2001	Francis Barany	19603/2615	8225

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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	**PAPER NUMBER**
1652	18

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,502	BARANY ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *16-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-47 are still at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-9 in Paper No. 7, 2/20/2003, is acknowledged. The traversal is on the ground(s) that the claims of the present application are closely related and therefore, require common areas of search and consideration and thus since no benefit is derived from imposing this restriction requirement, it should be withdrawn.

Applicants argument is not found persuasive because while the searches and considerations for each of the groups overlap, they are not coextensive. For example, search of Group III would require search of subclass 536/23.2 and search of Group V would require search of subclass 435/6. A search of each of these subclasses would be unnecessary the search of the elected group I. Further applicants are reminded that the previous restriction requirement was made using the lack of unity standard. Applicants are further reminded that the benefit derived from imposing this restriction requirement is that of increased quality of the patent which issues from the instant application as the searches and consideration necessary prior to allowance are significantly less.

It is noted that regardless of the above discussion it is believed that the thermostable ligases of Groups I –III should be combined. Thus the elected Group I should include claims 1-15.

The requirement is still deemed proper and is therefore made FINAL.

Claims 16-47 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 7.

Priority

Applicants claim of the benefit of U.S. Provisional application 60/106,461, filed October 30, 1998 is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

It is noted that currently no information disclosure statement exists in the application file.

Specification

The disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR

1.821 through 1.825 for the reason(s) set forth: The following portions of the specification list sequences which appear to meet the definition for a amino acid sequence, but do not have an associated SEQ ID NO: Figures 1B, 1C, the description of Figures 1A-C (i.e. "KXDG") and page 26, lines 15-19. Applicants attention is further directed to the MPEP 2422.02:

> **2422.02** The Requirement for Exclusive Conformance; Sequences Presented in Drawing Figures...It should be noted, though, that when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings.
>
> Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 1-15 are rejected under 35 U.S.C. § 101 because the claimed invention is directed toward non-statutory subject matter. In the absence of the hand of man, naturally occurring proteins including thermostable DNA ligases are considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). This rejection may be overcome by amending the claims to contain wording such as "An isolated and purified thermostable DNA ligase ..." .

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 10-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8, 10-15 are directed to all possible thermostable ligases having 100 fold higher fidelity than T4 ligase and 6 fold higher fidelity than wild-type *Thermus thermophilus* ligase, when sealing a ligation junction between a pair of oligonucleotide probes hybridized to a target sequence where there is a mismatch with the oligonucleotide probe having its 3' end abutting the ligation junction at the base immediately adjacent the ligation junction. The specification, however, only provides a single representative species isolated from *Thermus sp.* AK16D, having the amino acid sequence of SEQ ID NO: 1, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these enzymes by any identifying structural characteristics or properties other than the activities recited in claims 1, for which no predictability of structure is apparent. Further, applicants have only defined a single bacterium, *Thermus sp.* AK16D as a source of the claimed enzyme, while applicants claim all said enzymes having the recited functional limitation. Given this lack of additional representative species as encompassed by the

claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-8 and 10-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for thermostable DNA ligases having the amino acid sequence of SEQ ID NO: 1, does not reasonably provide enablement for any thermostable ligase having 100 fold higher fidelity than T4 ligase and 6 fold higher fidelity than wild-type *Thermus thermophilus* ligase, when sealing a ligation junction between a pair of oligonucleotide probes hybridized to a target sequence where there is a mismatch with the oligonucleotide probe having its 3' end abutting the ligation junction at the base immediately adjacent the ligation junction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-8 and 10-15 are so broad as to encompass any thermostable ligase having 100 fold higher fidelity than T4 ligase and 6 fold higher fidelity than wild-type *Thermus thermophilus* ligase, when sealing a ligation junction between a pair of oligonucleotide probes hybridized to a target sequence where there is a mismatch with the oligonucleotide probe having its 3' end abutting the ligation junction at the base immediately adjacent the ligation junction. The claims rejected under this section of U.S.C. 112, first paragraph, place minor (i.e. molecular weight of 78 to 81 kDa, or the presence of an arginine residue adjacent to the KXDG motif) if any structural limits on the claimed enzymes. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the thermostable DNA ligase from the *Thermus* sp. AK16D having the amino acid sequence of SEQ ID NO: 1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid

modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any thermostable ligase with the claimed functional limitations, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the claimed ligase activity (i.e. fidelity); (B) the general tolerance of thermostable DNA ligases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a thermostable DNA ligase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the ligase activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus having the claimed ligase (i.e. fidelity) activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any thermostable ligase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those thermostable ligases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1- 3 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Luo et al. (Nucleic Acids Research, Vol 24, No. 14, pp 3071-3078, 1996).

Luo et al. teach the identification and isolation of the mutant thermostable DNA ligases, K294R and K294P, which have an increased fidelity of approximately 4-fold and 11-fold relative to wild-type *Thermus thermophilus* (Tth) ligase, when sealing a ligation junction between a pair of oligonucleotide probes hybridized to a target sequence where there is a mismatch with the oligonucleotide probe having its 3' end

abutting the ligation junction at the base immediately adjacent the ligation junction. As Luo et al. further teach that the Tth DNA ligase has at least a 24-fold fidelity ration than that reported for T4 ligase, the mutant K29P DNA ligase has at least 100 fold higher fidelity than T4 DNA ligase. Thus the mutant thermostable DNA ligase taught by Luo et al. anticipates claims 1-3 and 8.

Claims 5, 10, 11 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Luo et al. (Nucleic Acids Research, Vol 24, No. 14, pp 3071-3078, 1996) as evidenced by Tong et al. (Nucleic Acids Research, Vol 27, No. 3, pp 788-794, 1999).

As discussed above, Luo et al. teach the identification and isolation of the mutant thermostable DNA ligases, K294R and K294P, which have an increased fidelity of approximately 4-fold and 11-fold relative to wild-type *Thermus thermophilus* (Tth) ligase, when sealing a ligation junction between a pair of oligonucleotide probes hybridized to a target sequence where there is a mismatch with the oligonucleotide probe having its 3' end abutting the ligation junction at the base immediately adjacent the ligation junction, thus anticipating claims 1-3 and 8. As Luo et al. further teach that the Tth DNA ligase has at least a 24-fold fidelity ration than that reported for T4 ligase, the mutant K29P DNA ligase has at least 100 fold higher fidelity than T4 DNA ligase.

The mutant thermostable DNA ligase, K294P, taught by Luo et al. which has at least 11-fold increased fidelity relative to wild type Tth DNA ligase, has at least 12 fold higher fidelity than wild-type *Tth* ligase in the presence of Mn^{2+} cofactor. While Luo et al. do not measure the fidelity of the mutant DNA ligase K294P in the presence of

Mn2+, such an increased level of fidelity relative to the wild-type DNA *Tth* ligase is an inherent property of the mutant DNA ligase K294P based on the evidentiary teachings of Tong et al. It is acknowledged that Tong et al. is not available as prior art, however, this is unnecessary as Tong et al. is merely used as an evidentiary reference to show an inherent property of the mutant DNA ligase taught by Luo et al. Tong et al. teach the fidelity factors of *Tth* ligase and T sp. AK16D ligase were reduced 12- and 6-fold respectively. Thus as the mutant DNA ligase K294P taught by Luo et al. has an increase of at least 11-fold in the absence of Mn2+, and it is a mutant of the wild-type *Tth* DNA ligase whose fidelity factor was reduced by 12-fold in the presence of Mn2+, it is thought that in the presence of Mn2+ the mutant DNA ligase taught by Luo et al. has a 12-fold higher fidelity than the wild-type *Tth* ligase. Thus claims 5, 10, 11 and 15 are anticipated by Luo et al. as evidenced by Tong et al.

Remarks

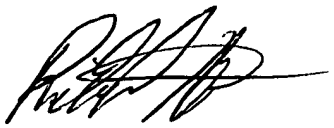
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax

phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
11/28/2003